

## REMARKS

The Official Action of October 24, 2001 and the prior art cited and relied upon therein have been carefully reviewed. The claims in the application are now claims 3-9, as claims 1, 2 and 10-14 have been withdrawn. Although claims 3-9 are incorrectly indicated as being allowed, no claims have actually been allowed. These claims define patentable subject matter warranting their allowance. Accordingly, Applicants respectfully request favorable reconsideration and allowance.

Claim 4 has been rejected under the second paragraph of §112 as being indefinite with regard to the claim language relative to chitosan. Upon review, Applicants agree. This claim has therefore been cancelled and replaced by claim 15, which correctly recites the referenced compounds.

Claims 3-5 and 9 are rejected under 35 USC 102(b) as being anticipated by Heindel et al. This rejection is respectfully traversed.

The Examiner states that Heindel et al. discloses the preparation of carboxymethyl dextran in an anhydrous non-nucleophilic solvent such as toluene, xylenes, diglyme or acetonitrile. While the Examiner focuses on said reference and its teachings, Applicants respectfully assert that attention must be paid to the fundamental differences in the reaction conditions described in the reference and those detailed in the instant specification. To this end for the purposes of clarification, claim 3 has been amended, obviating the 102 rejection.

Applicants call attention to the Heindel reference wherein the complete lactonization of carboxymethyl dextran is seen after as short a time period as five hours heating in acetonitrile (which has a boiling point of 82 degrees C). However, the

teaching of the present invention is, at least in part, directed to 24 hours of heating at temperatures of 150 degrees C in diglyme or mixed xylenes.

Furthermore, differences in the materials being compared, i.e. carboxymethyl dextran in the Heindel reference and carboxymethylcellulose in the examples of the current application must also be considered. Even the more drastic conditions detailed in the instant specification do not accomplish complete lactonization in all instances. And under the milder conditions described in the cited prior art, lactonization of pectin is undetectable and that of carboxymethylcellulose is substantially incomplete. Clearly, carboxymethyl dextran is considerably more facile in internal lactone formation than any of the other carbohydrates. The less vigorous procedures described by the Heindel reference to accomplish lactonization of carboxymethyl dextran are inoperable for other carbohydrate systems, possibly due to fundamental differences in primary and tertiary chemical structures.

Additionally, the Examiner concedes elsewhere in the Official Action that the Heindel reference does not describe the starting material as "finely ground", a limitation recited in claim 3.

For the above reasons and also in light of the claim amendment, reconsideration and withdrawal of the 102(b) rejection of claims 3-5 and 9 are respectfully requested.

Claim 9 is rejected under 35 USC 102(b) as being anticipated by Akanuma et al. This rejection is respectfully traversed.

The Examiner states that Akanuma discloses the preparation of carboxymethyl dextran lactone by thermal dehydration of CM-dextran and CM-cellulose

in non-nucleophilic solvent. As a threshold matter, Applicants note that lactone formation in this reference appears to occur entirely at room temperature. Additionally, Akanuma employs chemically-induced transformation using powerful dehydrating chemicals whose residue is capable of remaining with the matrix. This reference uses a rigid, highly cross-linked carbohydrate (here, Sephadex beads), unlike the non cross-linked families of the present invention. It must further be noted that Akanuma uses carbodiimide, thionyl chloride, or phosphorus pentachloride to achieve loss of water between a  $\text{-COOH}$  and an  $\text{-OH}$  to generate a presumed lactone in the polymer beads. It has been reported in the literature (see, e.g., 46 Intl. J. Cancer 1101 (1990) and 184 Anal. Biochem. 244 (1990)) that carbodiimides remain trapped by covalent adduct formation to carbohydrate hydroxyls. Such a consequence is highly undesirable for fabricating controlled release platforms for pharmaceuticals. Additionally, both thionyl chloride and phosphorus pentachloride are capable of fixing to and becoming trapped as inorganic esters.

Unlike the procedure taught by the Akanuma reference, thermal generation of the lactone as described in the instant application leaves no chemical residue as a signature. Thermal lactonization by the Applicants' method produces clear, non-colored products containing only C, H and O when their structures are analyzed. By contrast, the Akanuma method, especially when thionyl chloride or phosphorus pentachloride are employed, generates a red color (page 1358, right column). This is a clear signal to any skilled artisan that something other than simple lactone formation is occurring. Because the end use of the product in the Akanuma reference is a chromatography support, some entrapped impurities are tolerable. But when the intended

use is as a reactive polymer for close human use, as in the present application (e.g. in the case of a pharmaceutical carrier or a fragrance release matrix), high purity is a necessity.

Accordingly, reconsideration and withdrawal of the 102(b) rejection are respectfully requested.

Claim 9 is rejected under 35 USC 102(b) as being anticipated by Martey et al. This rejection is respectfully traversed.

The Examiner states that this reference discloses the dehydration of carboxymethylated dextran and cellulose to prepare a lactone product. Applicants wish to point out that the Martey reference is to a student work presented at an American Chemical Society meeting. It was, in fact, a report on the Heindel reference cited above. This abstract was submitted six months in advance of the meeting with the conceptual projection that cellulose lactonization might be demonstrated to occur under the five hours at 82 degrees C that was found for dextran lactonization. However, this projection was not borne out. No results from either cellulose or any other carbohydrates were in hand, no operable conditions were reported and no wavelengths for lactone adsorption were revealed. The Examiner writes: "Martey is silent on the identity of the solvent used." and Applicants state that this is for a good reason, as success had not been achieved. Applicants had discovered by experimentation that the cellulose system was simply a great deal less reactive than the dextran system.

Reconsideration and withdrawal of the 102(b) rejection of claim 9 are therefore respectfully requested.

Claims 3, 4 and 9 are rejected under 35 USC 103(a) as being unpatentable over Akanuma et al. This rejection is respectfully traversed. As discussed above,

because the Akanuma method does not employ heating in the lactonization step and because it yields such an unacceptably high level of impurities, this teaching would not render the present invention obvious to one of ordinary skill in the art.

It is well known that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference or references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. This is wholly lacking, as there would be no expectation that a method suitable for producing a chromatography platform would be appropriate for using on a pharmaceutical carrier. Second, there must be a reasonable expectation of success. As is well known to the Applicants, not all carbohydrates react equally well to mild lactonization conditions. The teaching of Akanuma of room temperature conditions may be considered quite mild. Finally, the prior art reference or references (when combined) must teach or suggest *all* the claim limitations. This is clearly lacking as well. For these reasons, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 3-6 and 9 are rejected under 35 USC 103(a) as being unpatentable over Heindel et al and Akanuma. This rejection is respectfully traversed.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use the Heindel process to lactonize CM-cellulose. Applicants have amply demonstrated the falsity of this proposition. The cellulose does not lactonize under the same conditions that can be used successfully with CM-dextran. Structural differences between the two compounds preclude the use of the Heindel method as published in 1994 for use with CM-cellulose. Additionally, Akanuma does not overcome

the deficiencies of the primary reference, as it discloses room temperature conditions for lactonization. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 3-9 are rejected under 35 USC 103a as being unpatentable over Heindel et al. and Akanuma et al. and further in view of Mill et al. This rejection is respectfully traversed.

The Examiner asserts that it would have been obvious to lactonize any biocompatible carboxylic polysaccharide using the Heindel process for their art-disclosed utility in the preparation of bioconjugates. Again, Applicants refer to the failure of the original Heindel disclosure in lactonizing carbohydrates other than dextran. A study by Heymann on the elasticity and flexibility of dextran, starch and cellulose (to be accessed at <http://www.mpibc.gwdg.de/abteilungen/071/sugar.html>) demonstrates the profound differences between these substances. Not only is dextran the most flexible and elastic substance, but the authors reported "...no significant effect of solvent, especially not on the elastic properties." In the article "Survey of Biopolymers" by BeMiller found in the Kirk-Othmer Encyclopedia of Chemical Technology (1993), it is noted that dextran is virtually unique among polysaccharides in that it is generated at high molecular weight, is very water soluble and is a rare bio-polymer derived from microbial fermentation. By contrast, cellulose is highly water insoluble, is derived from higher plants and exists as a coiled internally hydrogen-bonded polymer unless solubilized in such solvents as copper ammonium or strong hydroxide.

These striking molecular differences extend also to the carboxymethyl derivatives. Carboxymethyl dextran forms highly stable hydrogels that coat chip surfaces

and prevent non-specific binding of biomolecules (see, e.g., <http://www.xantec.com/html/asisensorchips.html>), but no such characteristics are reported for CM-cellulose. Carboxymethyl dextran lactone dries to a white solid, whereas carboxymethylcellulose lactone dries to a strong, clear film.

Conditions to ring-open the carboxymethylcellulose lactone and attach pharmaceuticals and fragrances can also not be deduced from the conditions usable with dextran. Some slowly reacting nucleophiles require long reaction times, with none being as short as the five hours disclosed in the Heindel et al. prior art reference cited by the Examiner. In some cases, an inert atmosphere of argon is required, as in Examples 11-14 of the instant application. In other cases, an argon blanket is not required, as in the case when the nucleophile is an alcohol or a carboxylic acid, as seen in Examples 15-17 of the instant application.

For these reasons, reconsideration and withdrawal of the rejection are respectfully requested.

It is submitted that the pending claims are free of the prior art and that all rejections have been addressed. Favorable reconsideration and allowance are earnestly solicited.

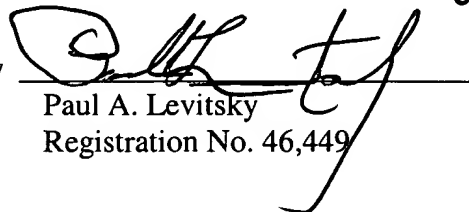
Respectfully submitted,

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